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PharmGKB summary: ondansetron and tropisetron pathways, pharmacokinetics and pharmacodynamics

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Background

Ondansetron and tropisetron are first-generation serotonin (5-hydroxytryptamine or 5-HT) receptor antagonists which bind to the 5-HT₃ receptor. Although ondansetron is a carbazole compound while tropisetron is an indole compound, their carbon and nitrogen rings give both molecules a structural similarity to serotonin, allowing them to bind to the 5-HT₃ receptor and exert their clinical effect [1–3].

Ondansetron and tropisetron can be used either alone or in combination with other antiemetics to reduce nausea and vomiting in patients who have undergone surgery or chemotherapy [1, 4–6]. They have similar efficacies to each other and to the other 5-HT₃ receptor antagonists with the exception of granisetron, which has been shown to have a higher efficacy in some studies [7–12]. They also have similar side effect profiles, with the most common side effects being headache, dizziness and diarrhea [7, 13]. There are also reports of cardiac effects being caused by these molecules, particularly ondansetron [1, 13].

It should be noted that the vast majority of relevant literature pertains to ondansetron rather than tropisetron, reflecting the fact that ondansetron is more commonly prescribed than tropisetron. Therefore, much of the focus of this review will be on ondansetron.

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Pharmacokinetics

Ondansetron and tropisetron are generally available as an oral tablet [14–17]. Other administration forms, including injectable formulations, have been investigated but, at the time of writing, are not being marketed [18–24]. Oral ondansetron and tropisetron both have a T_{max} of around 3 hours [19, 25]. Ondansetron has a plasma half-life between 3–6 hours while the half-life of tropisetron is around 6 hours [15–17, 26–28]. Strikingly, there is no correlation between plasma concentrations of ondansetron and the level of efficacy. Pharmacodynamic factors, rather than pharmacokinetic factors, are considered to be more likely to affect efficacy, as discussed in the Pharmacodynamics section below. [26, 29–32].

The clearance of ondansetron decreases with age in both pediatric and adult subjects [26, 28, 33–35]. Elderly subjects have an increased C_{max} and AUC of ondansetron compared to younger subjects, possibly due to an age-related reduction in hepatic function. Elderly subjects also had an increased volume of distribution at steady-state dosing and an increased elimination half-life [26, 34, 35]. The exception to this general trend is in subjects under 6 months of age, who have a decreased clearance of ondansetron compared to older pediatric subjects [36, 37]. This is likely due to the fact that CYP3A4, which is considered to mediate the majority of ondansetron metabolism, has reduced activity in infants under 6 months old [38, 39]. Age does not affect tropisetron pharmacokinetics [40].

Plasma clearance of ondansetron is significantly reduced in patients with hepatic impairment, leading to an increased AUC and half-life in these patients compared to healthy controls [41, 42]. Similarly, patients with liver cirrhosis had reduced metabolic clearance of tropisetron while patients with moderate or severe renal impairment had reduced non-renal clearance of tropisetron [40]. However, tropisetron pharmacokinetics were not altered in patients with hepatitis or fatty liver disease [40].

Studies of the pharmacokinetics of oral forms of ondansetron have suggested that there are possible sex-based differences in ondansetron metabolism. Women were found to have a significantly increased C_{max} , AUC and bioavailability of ondansetron compared to men [27, 35].

The pharmacokinetics of ondansetron during pregnancy have been investigated. In a case study of one pregnant subject, oral clearance of ondansetron increased over the course of gestation, causing a decrease in both the C_{max} and the AUC_{0-8} [43]. Ondansetron has also been found to cross the placenta during the early stage of pregnancy and can be found in fetal tissue and amniotic fluid. However, it should be noted that ondansetron is not considered to cause fetal abnormalities [36, 44].

As ondansetron is commonly prescribed to control chemotherapy-induced nausea and vomiting (CINV), it is important to understand any interactions between ondansetron and chemotherapeutic agents. Although ondansetron pharmacokinetics appear to be unaffected by the presence of chemotherapeutic agents [45], there is evidence that ondansetron can alter the pharmacokinetic parameters of chemotherapy. Oncology patients receiving either cisplatin or cyclophosphamide and concomitant ondansetron had decreased AUCs of both chemotherapeutic agents compared to patients who were not taking ondansetron [46, 47].

The exact reason for this interaction is not known but may involve CYP3A inhibition in the case of cyclophosphamide [47]. In contrast to ondansetron, tropisetron was found to increase the C_{max} and AUC of a number of chemotherapeutic agents in pediatric patients [48]. The potential clinical effects of these interactions remain to be studied in greater detail.

A number of other drug-drug interactions involving ondansetron have been reported. The neurokinin-1 receptor antagonist aprepitant is often given in combination with a 5-HT₃ receptor antagonist such as ondansetron to control nausea and vomiting. In a crossover study of 19 patients given both aprepitant and ondansetron or ondansetron alone found that aprepitant can cause a ~15% increase in the AUC of ondansetron when administered concomitantly [49]. This seems to be most likely due to aprepitant's role as a moderate CYP3A4 inhibitor [50], however this interaction is not thought to have a resulting clinical effect on patients [51].

Conversely, rifampin reduces exposure to both oral and intravenous ondansetron by significantly reducing both the AUC and half-life of ondansetron. It also reduces the bioavailability of ondansetron by 33%. This is thought to be due to induction of CYP3A4 and possibly CYP1A2 by rifampin [52].

Absorption and distribution

Oral ondansetron and tropisetron have a bioavailability of around 60% and are rapidly absorbed into the plasma following administration [17, 26, 40, 52]. Exposure to ondansetron is increased by approximately 17% when it is administered following food [53]. Once absorbed, around 80% of ondansetron is found bound to plasma proteins [42, 54], with reduced binding seen in patients with hepatic impairment [42]. Tropisetron exhibits a more moderate protein binding behavior of between 59–71% [40].

Metabolism

Figure 1 shows the metabolism and pharmacodynamics of ondansetron. Ondansetron is subject to first-pass metabolism in the liver [42, 55]. Following this, it is primarily metabolized by hydroxylation at the 6, 7 or 8 positions of the indole ring [56, 57] with some minor metabolites also formed, including N-demethylondansetron [58]. These minor metabolites can be detected in serum but 7-hydroxyondansetron and 8-hydroxyondansetron tend to be the predominant ones [56, 59]. These hydroxylated metabolites can then be subsequently glucuronidated or sulfated [56].

The metabolism of ondansetron is carried out by multiple enzymes, including CYP1A1/2, CYP3A and CYP2D6 [58]. Although CYP3A is considered to mediate the majority of ondansetron metabolism [38], formation of the metabolites 7-hydroxyondansetron and 8-hydroxyondansetron appears to be mostly carried out by the enzyme CYP1A2, indicated by the star icon on the pathway image [38]. CYP2D6 also has a minor role in the hydroxylation of ondansetron, mediating approximately 30% of total ondansetron metabolism [38, 58, 60].

The different contributions of CYP3A and CYP2D6 to ondansetron metabolism can be explained by the differences in ondansetron's binding affinity to each enzyme. Ondansetron

forms four π - π stacking interactions with CYP3A4, resulting in an increased binding affinity compared to that for CYP2D6, where ondansetron only forms one π - π stacking interaction and a hydrogen bond [61].

It should be noted that many *in vitro* experiments which investigate ondansetron metabolism use concentrations of ondansetron which are higher than the peak plasma concentrations of ondansetron seen *in vivo* [58, 62]. Caution should therefore be used when extrapolating the results of these *in vitro* experiments to ondansetron metabolism *in vivo*. Indeed, at least one study has found that data from *in vitro* metabolism experiments have little correlation with data from *in vivo* experiments [59].

Figure 2 shows the metabolism and pharmacodynamics of tropisetron. In a similar manner to ondansetron, the main route of tropisetron metabolism is by hydroxylation with subsequent sulfation and glucuronidation of the hydroxylated metabolites [16, 40]. Hydroxylation of tropisetron can occur at the 5, 6 or 7 positions of the drug's indole ring, with 5-hydroxytropisetron and 6-hydroxytropisetron being the predominant metabolites [40, 63]. In contrast to ondansetron metabolism, up to 91% of tropisetron metabolism is carried out by CYP2D6 with a minor contribution from CYP3A4, again shown on the pathway image by the presence of the star icon next to CYP2D6 [58, 60, 63].

Work in human liver microsomes has suggested that N-demethyltropisetron may also be formed by CYP3A4 in addition to an N-oxide metabolite and several other unidentified minor metabolites. However, these metabolites have yet to be detected *in vivo* [58, 63].

Excretion

Around 10% of the original dose of both ondansetron and tropisetron are excreted unchanged in the urine [16, 26, 40]. Between 44–53% of a dose of ondansetron is excreted in the urine as either ondansetron or its metabolites within 24 hours of administration [26]. About 15% of a dose of tropisetron is excreted as metabolites in the feces, with a further 70% excreted as metabolites in the urine [16, 40].

Pharmacodynamics

Ondansetron and tropisetron prevent the binding of serotonin released from intestinal enterochromaffin cells to 5-HT₃ receptors on adjacent vagal afferent nerves, as shown in Figure 1 and Figure 2. This blockade of 5-HT₃ receptors reduces nausea and vomiting by decreasing vagus nerve signaling and the subsequent release of serotonin in the brainstem [64]. It is important to note that serotonin signaling is not the only mechanism by which nausea and vomiting can be stimulated and, as a result, ondansetron and tropisetron cannot be used to treat all cases of nausea and vomiting [64].

Tropisetron has been found to occupy more 5-HT₃ receptors (78%) on average than ondansetron (50%) yet both molecules are similarly effective in terms of preventing vomiting [30]. As with the plasma concentrations of these two drugs, there are large interindividual differences in 5-HT₃ receptors occupancy. However, the efficacy of each drug appears to be, at least partially, correlated to the level of 5-HT₃ receptor occupancy [29, 30].

The binding of ondansetron to the 5-HT₃ receptor has been studied in some detail. Work using the murine 5-HT₃ receptor has shown that binding is mediated by cation- π interactions between ondansetron and the Trp183 residue of the receptor. This is a similar mode of binding as when serotonin binds to the 5-HT₃ receptor [65]. Unlike palonosetron, another 5-HT₃ receptor antagonist, binding of ondansetron does not cause internalization of the 5-HT₃ receptor [66].

In vitro work using a range of animal and human proteins suggest that, in addition to binding to the 5-HT₃ receptor, both ondansetron and tropisetron may interact with other receptors and transporters, such as MATE1 [67–71]. However, the relevance of these findings to the actions of either ondansetron or tropisetron in humans has yet to be determined.

There is a documented pharmacodynamic interaction between ondansetron and serotonin reuptake inhibitors (SRIs), such as fluoxetine, which can lead to serotonin syndrome, where a patient experiences symptoms such as hyperthermia, agitation and tremor as a result of increased serotonin levels [72]. Patients receiving ondansetron to treat CINV and a concomitant SRI were more likely to experience vomiting episodes than patients who had never been treated with an SRI, suggesting that SRIs reduce the efficacy of ondansetron [73, 74]. This is thought to be due to increased levels of free serotonin as a result of the action of the SRI, which increases competition between serotonin and ondansetron for binding to serotonin receptors. Conversely, ondansetron has been found to augment the actions of SRIs and could be useful for the treatment of conditions such as obsessive-compulsive disorder in patients who have not responded to SRI treatment alone [75–77].

Ondansetron has also been found to affect tramadol requirements in patients, with patients taking concomitant tramadol and ondansetron having decreased analgesia and increased tramadol dose requirements compared to patients taking tramadol only [78–81]. However, it should be noted that not all studies have replicated this observation [82]. It has been postulated that the decrease in tramadol analgesia is due to blockade of 5-HT₃ receptors by ondansetron, which prevents the binding of serotonin molecules released by the actions of tramadol [78].

Ondansetron is known to prolong the QT interval of patients in a dose-dependent manner [83, 84]. Work on the effects of ondansetron and tropisetron on cardiac ion channels suggests that both molecules are able to interact with the inactive state of the cardiac sodium channel Na_v1.5. Na_v1.5 is encoded for by the gene *SCN5A*. This interaction causes the channel to become blocked, with tropisetron having a greater effect than ondansetron [85, 86]. Ondansetron has also been found to be capable of blocking cardiac potassium channels with an increased affinity for these channels over sodium channels [85].

Pharmacogenetics

Variation in CYP2D6 activity can impact on the pharmacokinetics of ondansetron and tropisetron, ultimately affecting the efficacy of these drugs. CYP2D6 ultrarapid metabolizers (UMs) have decreased exposure and a reduced response to both ondansetron and tropisetron, as measured by an increased number of vomiting episodes following treatment compared to

CYP2D6 normal metabolizers (NMs) [87–89]. As a result, the Clinical Pharmacogenetics Implementation Consortium (CPIC) have published a clinical guideline advising that CYP2D6 UMs are prescribed alternative antiemetic medication, such as dolasetron [90].

The response of CYP2D6 intermediate and poor metabolizers (IMs and PMs) to ondansetron and tropisetron is less clear. While some work has indicated that IMs and PMs have an increased exposure to ondansetron and tropisetron [87, 89, 91], a notable effect of these phenotypes on a patient's response has not been documented [89]. In addition, other studies have found no effect of a PM or IM phenotype on the efficacy or pharmacokinetic parameters of the molecules [92, 93]. It should be noted that Perwitasari *et al.* did not identify any CYP2D6 PMs in their cohort.

Detailed analysis of the effect of variation in CYP2D6 and CYP3A5 activity on ondansetron pharmacokinetics has found that genetic variation in *CYP2D6* affect exposure to the S-ondansetron enantiomer, but not R-ondansetron [91]. By contrast, the AUC of R-ondansetron was increased in patients carrying the non-functional *CYP3A5**3 allele [91].

The synonymous variant rs1045642 in *ABCB1* may affect ondansetron efficacy with the G allele associated with a reduced response to ondansetron while patients carrying the TT genotype were more likely to be free of vomiting following ondansetron treatment [92, 94, 95]. One study has expanded on this and found that the CTG haplotype consisting of the variants rs1045642, rs2032582 and rs1128503 is associated with a reduced response to ondansetron. Tropisetron does not appear to be affected by rs1045642 [95].

Work on the relationship between the transporter SLC22A1 and the efficacy of ondansetron and tropisetron has found that patients who do not have any active *SLC22A1* alleles may experience an increased efficacy of both drugs [96]. The authors of this paper suggest that a lack of active *SLC22A1* alleles reduces hepatic cellular uptake and therefore metabolism and inactivation of tropisetron. However, *in vitro* work by the same group indicated that SLC22A1 was not involved in ondansetron transport [96]. The conflicting results warrant further investigations to determine the role of SLC22A1 on ondansetron exposure.

A study into the effects of polymorphisms in the *HTR3A* gene, which encodes the 5-HT_{3A} subunit of the 5-HT₃ receptor, found no statistically significant effects of any variants on the efficacy of either ondansetron or tropisetron [97]. Tremblay *et al.* found that homozygotes for the del allele of rs45460698 in the promotor of *HTR3B*, which encodes the 5-HT_{3B} subunit of the 5-HT₃ receptor, had significantly more episodes of vomiting when treated with ondansetron or tropisetron compared to heterozygotes or homozygotes for the AAG allele [98]. However, this association lost significance following multiple testing correction at one of the two timepoints assessed. Both Tremblay *et al.* and Perwitasari *et al.* noted nonsignificant trends for rs45460698 heterozygotes to have increased nausea and vomiting following ondansetron or tropisetron therapy compared to AAG homozygotes [92, 98].

Conclusion

The pharmacokinetics and pharmacodynamics of ondansetron and tropisetron are fairly well characterized, although there is an absence of information about the transport of both drugs.

While there is clinical guidance regarding the use of ondansetron and tropisetron in CYP2D6 UMs, further work is warranted to elucidate whether the CYP2D6 PM phenotype has an impact on a patient's response to either drug and to identify additional variants in other metabolizing enzymes, such as CYP1A2, which may have an impact on patient response.

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References

1. Kovac AL, Comparative Pharmacology and Guide to the Use of the Serotonin 5-HT₃ Receptor Antagonists for Postoperative Nausea and Vomiting. *Drugs*, 2016 76(18): p. 1719–1735. [PubMed: 27988869]
2. Kovac AL, Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. *Drug Saf*, 2003 26(4): p. 227–59. [PubMed: 12608887]
3. Lee CR, Plosker GL, and McTavish D, Tropisetron. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as an antiemetic. *Drugs*, 1993 46(5): p. 925–43. [PubMed: 7507039]
4. Lazarus HM, et al., Antiemetic efficacy and pharmacokinetic analyses of the serotonin antagonist ondansetron (GR 38032F) during multiple-day chemotherapy with cisplatin prior to autologous bone marrow transplantation. *J Natl Cancer Inst*, 1990 82(22): p. 1776–8. [PubMed: 2146401]
5. Cubeddu LX, et al., Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med*, 1990 322(12): p. 810–6. [PubMed: 1689807]
6. Apfel CC, et al., A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med*, 2004 350(24): p. 2441–51. [PubMed: 15190136]
7. Abali H and Celik I, Tropisetron, ondansetron, and granisetron for control of chemotherapy-induced emesis in Turkish cancer patients: a comparison of efficacy, side-effect profile, and cost. *Cancer Invest*, 2007 25(3): p. 135–9. [PubMed: 17530482]
8. Aksoylar S, et al., Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. *Pediatr Hematol Oncol*, 2001 18(6): p. 397–406. [PubMed: 11554235]
9. del Giglio A, et al., Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting: results of a meta-analysis of randomized controlled trials. *Cancer*, 2000 89(11): p. 2301–8. [PubMed: 11147601]
10. Fox-Geiman MP, et al., Double-blind comparative trial of oral ondansetron versus oral granisetron versus IV ondansetron in the prevention of nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation. *Biol Blood Marrow Transplant*, 2001 7(11): p. 596–603. [PubMed: 11760147]
11. Gregory RE and Ettinger DS, 5-HT₃ receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. *Drugs*, 1998 55(2): p. 173–89. [PubMed: 9506240]
12. Jordan K, et al., A meta-analysis comparing the efficacy of four 5-HT₃-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer*, 2007 15(9): p. 1023–33. [PubMed: 17205281]
13. Goodin S and Cunningham R, 5-HT₃-receptor antagonists for the treatment of nausea and vomiting: a reappraisal of their side-effect profile. *Oncologist*, 2002 7(5): p. 424–36. [PubMed: 12401905]
14. Cohen IT, et al., Ondansetron oral disintegrating tablets: acceptability and efficacy in children undergoing adenotonsillectomy. *Anesth Analg*, 2005 101(1): p. 59–63, table of contents. [PubMed: 15976206]

15. Claybon L, Single dose intravenous ondansetron for the 24-hour treatment of postoperative nausea and vomiting. *Anaesthesia*, 1994 49 Suppl: p. 24–9. [PubMed: 8129159]
16. Fischer V, Baldeck JP, and Tse FL, Pharmacokinetics and metabolism of the 5-hydroxytryptamine antagonist tropisetron after single oral doses in humans. *Drug Metab Dispos*, 1992 20(4): p. 603–7. [PubMed: 1356742]
17. Kees F, et al., Pharmacokinetics of therapeutic doses of tropisetron in healthy volunteers. *Br J Clin Pharmacol*, 2001 52(6): p. 705–7. [PubMed: 11736884]
18. Cho E, Gwak H, and Chun I, Formulation and evaluation of ondansetron nasal delivery systems. *Int J Pharm*, 2008 349(1–2): p. 101–7. [PubMed: 17822864]
19. Dadey E, Bioequivalence of ondansetron oral soluble film 8 mg (ZUPLENZ) and ondansetron orally disintegrating tablets 8 mg (ZOFRAN) in healthy adults. *Am J Ther*, 2015 22(2): p. 90–7. [PubMed: 25581856]
20. Dychter SS, et al., Tolerability and pharmacokinetic properties of ondansetron administered subcutaneously with recombinant human hyaluronidase in minipigs and healthy volunteers. *Clin Ther*, 2014 36(2): p. 211–24. [PubMed: 24486335]
21. Patel DR, et al., Development and in-vivo evaluation of ondansetron gels for transdermal delivery. *Drug Dev Ind Pharm*, 2015 41(6): p. 1030–6. [PubMed: 24919508]
22. Silva SM, et al., A combination of nonionic surfactants and iontophoresis to enhance the transdermal drug delivery of ondansetron HCl and diltiazem HCl. *Eur J Pharm Biopharm*, 2012 80(3): p. 663–73. [PubMed: 22137964]
23. Zhu Y, et al., Pharmacokinetics and bioavailability study of two ondansetron oral soluble film formulations in fasting healthy male Chinese volunteers. *Drug Des Devel Ther*, 2015 9: p. 4621–9.
24. Mahajan HS and Gattani SG, Nasal administration of ondansetron using a novel microspheres delivery system Part II: ex vivo and in vivo studies. *Pharm Dev Technol*, 2010 15(6): p. 653–7. [PubMed: 20020823]
25. Deng P, Zhong D, and Chen X, Determination of tropisetron in human plasma by liquid chromatography-tandem mass spectrometry. *J Pharm Biomed Anal*, 2009 49(3): p. 848–52. [PubMed: 19200686]
26. Blackwell CP and Harding SM, The clinical pharmacology of ondansetron. *Eur J Cancer Clin Oncol*, 1989 25 Suppl 1: p. S21–4; discussion S25–7.
27. Lam YW, et al., Relative bioavailability of an extemporaneous ondansetron 4-mg capsule formulation versus solution. *Pharmacotherapy*, 2004 24(4): p. 477–81. [PubMed: 15098801]
28. GlaxoSmithKline, Zofran Prescribing Information Revised 3 2017.
29. Yamada Y, et al., Receptor occupancy theory-based analysis of antiemetic effects and standard doses of 5-HT₃ receptor antagonists in cancer patients. *Cancer Chemother Pharmacol*, 2004 54(2): p. 185–90. [PubMed: 15168080]
30. Ayuhara H, et al., Receptor occupancy theory-based analysis of interindividual differences in antiemetic effects of 5-HT₃ receptor antagonists. *Int J Clin Oncol*, 2009 14(6): p. 518–24. [PubMed: 19967488]
31. Grunberg SM, et al., Correlation of anti-emetic efficacy and plasma levels of ondansetron. *Eur J Cancer*, 1990 26(8): p. 879–82. [PubMed: 2145930]
32. Musshoff F, et al., Enantioselective determination of ondansetron and 8-hydroxyondansetron in human plasma from recovered surgery patients by liquid chromatography-tandem mass spectrometry. *J Anal Toxicol*, 2010 34(9): p. 581–6. [PubMed: 21073811]
33. Spahr-Schopfer IA, et al., Pharmacokinetics of intravenous ondansetron in healthy children undergoing ear, nose, and throat surgery. *Clin Pharmacol Ther*, 1995 58(3): p. 316–21. [PubMed: 7554705]
34. Colthup PV, et al., Determination of ondansetron in plasma and its pharmacokinetics in the young and elderly. *J Pharm Sci*, 1991 80(9): p. 868–71. [PubMed: 1839313]
35. Pritchard JF, et al., Age and gender effects on ondansetron pharmacokinetics: evaluation of healthy aged volunteers. *Clin Pharmacol Ther*, 1992 51(1): p. 51–5. [PubMed: 1531044]
36. Elkomy MH, et al., Ondansetron pharmacokinetics in pregnant women and neonates: towards a new treatment for neonatal abstinence syndrome. *Clin Pharmacol Ther*, 2015 97(2): p. 167–76. [PubMed: 25670522]

37. Mondick JT, et al., Population pharmacokinetics of intravenous ondansetron in oncology and surgical patients aged 1–48 months. *Eur J Clin Pharmacol*, 2010 66(1): p. 77–86. [PubMed: 19798490]
38. Dixon CM, et al., Multiple forms of cytochrome P450 are involved in the metabolism of ondansetron in humans. *Drug Metab Dispos*, 1995 23(11): p. 1225–30. [PubMed: 8591723]
39. Edginton AN, et al., A mechanistic approach for the scaling of clearance in children. *Clin Pharmacokinet*, 2006 45(7): p. 683–704. [PubMed: 16802850]
40. de Bruijn KM, Tropisetron. A review of the clinical experience. *Drugs*, 1992 43 Suppl 3: p. 11–22.
41. Blake JC, et al., The pharmacokinetics of intravenous ondansetron in patients with hepatic impairment. *Br J Clin Pharmacol*, 1993 35(4): p. 441–3. [PubMed: 8485026]
42. Figg WD, et al., Pharmacokinetics of ondansetron in patients with hepatic insufficiency. *J Clin Pharmacol*, 1996 36(3): p. 206–15. [PubMed: 8690814]
43. Lemon LS, et al., Ondansetron Exposure Changes in a Pregnant Woman. *Pharmacotherapy*, 2016 36(9): p. e139–41. [PubMed: 27374186]
44. Siu SS, Chan MT, and Lau TK, Placental transfer of ondansetron during early human pregnancy. *Clin Pharmacokinet*, 2006 45(4): p. 419–23. [PubMed: 16584287]
45. Hsyu PH, et al., Oral ondansetron pharmacokinetics: the effect of chemotherapy. *J Clin Pharmacol*, 1994 34(7): p. 767–73. [PubMed: 7929872]
46. Cagnoni PJ, et al., Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin by antiemetics. *Bone Marrow Transplant*, 1999 24(1): p. 1–4. [PubMed: 10435726]
47. Gilbert CJ, et al., Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer. *Cancer Chemother Pharmacol*, 1998 42(6): p. 497–503. [PubMed: 9788577]
48. Gaedick G, et al., Pharmacokinetics of the 5HT₃ receptor antagonist tropisetron in children. *Pediatr Hematol Oncol*, 1996 13(5): p. 405–16. [PubMed: 10897812]
49. Blum RA, et al., Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. *Clin Ther*, 2003 25(5): p. 1407–19. [PubMed: 12867217]
50. Majumdar AK, et al., Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe. *Clin Pharmacol Ther*, 2003 74(2): p. 150–6. [PubMed: 12891225]
51. Stoch SA, et al., Double-blind crossover study to assess potential differences in cytochrome P450 3A4 activity in healthy subjects receiving ondansetron plus dexamethasone, with and without aprepitant. *Cancer Chemother Pharmacol*, 2011 67(6): p. 1313–21. [PubMed: 20734049]
52. Villikka K, Kivisto KT, and Neuvonen PJ, The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther*, 1999 65(4): p. 377–81. [PubMed: 10223773]
53. Bozigian HP, et al., Ondansetron absorption in adults: effect of dosage form, food, and antacids. *J Pharm Sci*, 1994 83(7): p. 1011–3. [PubMed: 7965657]
54. B S, et al., Exploring the binding mechanism of ondansetron hydrochloride to serum albumins: spectroscopic approach. *Spectrochim Acta A Mol Biomol Spectrosc*, 2012 86: p. 410–6. [PubMed: 22112579]
55. Board T and Board R, The role of 5-HT₃ receptor antagonists in preventing postoperative nausea and vomiting. *Aorn j*, 2006 83(1): p. 209–16, 219–20. [PubMed: 16528908]
56. Saynor DA and Dixon CM, The metabolism of ondansetron. *Eur J Cancer Clin Oncol*, 1989 25 Suppl 1: p. S75–7. [PubMed: 2533904]
57. Xu X, Bartlett MG, and Stewart JT, Determination of ondansetron and its hydroxy metabolites in human serum using solid-phase extraction and liquid chromatography/positive ion electrospray tandem mass spectrometry. *J Mass Spectrom*, 2000 35(11): p. 1329–34. [PubMed: 11114092]
58. Fischer V, et al., The polymorphic cytochrome P-4502D6 is involved in the metabolism of both 5-hydroxytryptamine antagonists, tropisetron and ondansetron. *Drug Metab Dispos*, 1994 22(2): p. 269–74. [PubMed: 8013282]
59. Somers GI, et al., The metabolism of the 5HT₃ antagonists ondansetron, alosetron and GR87442 I: a comparison of in vitro and in vivo metabolism and in vitro enzyme kinetics in rat, dog and human hepatocytes, microsomes and recombinant human enzymes. *Xenobiotica*, 2007 37(8): p. 832–54. [PubMed: 17701832]

60. Sanwald P, David M, and Dow J, Use of electrospray ionization liquid chromatography-mass spectrometry to study the role of CYP2D6 in the in vitro metabolism of 5-hydroxytryptamine receptor antagonists. *J Chromatogr B Biomed Appl*, 1996 678(1): p. 53–61. [PubMed: 8861656]
61. Lewis DF, et al., An evaluation of ondansetron binding interactions with human cytochrome P450 enzymes CYP3A4 and CYP2D6. *Drug Metab Lett*, 2010 4(1): p. 25–30. [PubMed: 20201779]
62. Blower PR, 5-HT₃-receptor antagonists and the cytochrome P450 system: clinical implications. *Cancer J*, 2002 8(5): p. 405–14. [PubMed: 12416899]
63. Firkusny L, Kroemer HK, and Eichelbaum M, In vitro characterization of cytochrome P450 catalysed metabolism of the antiemetic tropisetron. *Biochem Pharmacol*, 1995 49(12): p. 1777–84. [PubMed: 7598739]
64. Endo T, et al., Neurochemistry and neuropharmacology of emesis - the role of serotonin. *Toxicology*, 2000 153(1–3): p. 189–201. [PubMed: 11090957]
65. Duffy NH, Lester HA, and Dougherty DA, Ondansetron and granisetron binding orientation in the 5-HT₃ receptor determined by unnatural amino acid mutagenesis. *ACS Chem Biol*, 2012 7(10): p. 1738–45. [PubMed: 22873819]
66. Rojas C, et al., Palonosetron triggers 5-HT₃ receptor internalization and causes prolonged inhibition of receptor function. *Eur J Pharmacol*, 2010 626(2–3): p. 193–9. [PubMed: 19836386]
67. van Wijngaarden I, Tulp MT, and Soudijn W, The concept of selectivity in 5-HT receptor research. *Eur J Pharmacol*, 1990 188(6): p. 301–12. [PubMed: 2164935]
68. Macor JE, et al., The 5-HT₃ antagonist tropisetron (ICS 205–930) is a potent and selective alpha₇ nicotinic receptor partial agonist. *Bioorg Med Chem Lett*, 2001 11(3): p. 319–21. [PubMed: 11212100]
69. Paul M, et al., Antiemetics of the 5-hydroxytryptamine 3A antagonist class inhibit muscle nicotinic acetylcholine receptors. *Anesth Analg*, 2005 101(3): p. 715–21, table of contents. [PubMed: 16115980]
70. Hur W, et al., Ondansetron attenuates the activity of excitatory amino acid transporter type 3 expressed in *Xenopus* oocytes. *Eur J Pharmacol*, 2014 733: p. 7–12. [PubMed: 24690261]
71. Wittwer MB, et al., Discovery of potent, selective multidrug and toxin extrusion transporter 1 (MATE1, SLC47A1) inhibitors through prescription drug profiling and computational modeling. *J Med Chem*, 2013 56(3): p. 781–795. [PubMed: 23241029]
72. Alusik S, Kalatova D, and Paluch Z, Serotonin syndrome. *Neuro Endocrinol Lett*, 2014 35(4): p. 265–73. [PubMed: 25038602]
73. Mir O, et al., Interaction between serotonin reuptake inhibitors, 5-HT₃ antagonists, and NK1 antagonists in cancer patients receiving highly emetogenic chemotherapy: a case-control study. *Support Care Cancer*, 2012 20(9): p. 2235–9. [PubMed: 22644261]
74. Koriech OM, Fluoxetine treatment comprises the antiemetic efficacy of ondansetron in cancer patients. *Clin Oncol (R Coll Radiol)*, 1995 7(6): p. 371–2. [PubMed: 8590698]
75. Betry C, et al., A 5-HT₃ receptor antagonist potentiates the behavioral, neurochemical and electrophysiological actions of an SSRI antidepressant. *Pharmacol Biochem Behav*, 2015 131: p. 136–42. [PubMed: 25697477]
76. Heidari M, et al., Ondansetron or placebo in the augmentation of fluvoxamine response over 8 weeks in obsessive-compulsive disorder. *Int Clin Psychopharmacol*, 2014 29(6): p. 344–50. [PubMed: 24850229]
77. Pallanti S, et al., Ondansetron augmentation in patients with obsessive-compulsive disorder who are inadequate responders to serotonin reuptake inhibitors: improvement with treatment and worsening following discontinuation. *Eur Neuropsychopharmacol*, 2014 24(3): p. 375–80. [PubMed: 24406025]
78. Arcioni R, et al., Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT₃ spinal receptor involvement in acute pain in humans. *Anesth Analg*, 2002 94(6): p. 1553–7. [PubMed: 12032025]
79. De Witte JL, et al., The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg*, 2001 92(5): p. 1319–21. [PubMed: 11323369]
80. Vale C, et al., Co-administration of ondansetron decreases the analgesic efficacy of tramadol in humans. *Pharmacology*, 2011 88(3–4): p. 182–7. [PubMed: 21952250]

81. Stevens AJ, Woodman RJ, and Owen H, The effect of ondansetron on the efficacy of postoperative tramadol: a systematic review and meta-analysis of a drug interaction. *Anaesthesia*, 2015 70(2): p. 209–18. [PubMed: 25490944]
82. Rauers NI, et al., Antagonistic effects of ondansetron and tramadol? A randomized placebo and active drug controlled study. *J Pain*, 2010 11(12): p. 1274–81. [PubMed: 20488759]
83. Lee JH, et al., The effect of sevoflurane and ondansetron on QT interval and transmural dispersion of repolarization in children. *Paediatr Anaesth*, 2014 24(4): p. 421–5. [PubMed: 24372925]
84. Kim SH, et al., Effects of prophylactic ramosetron and ondansetron on corrected QT interval during general anesthesia. *J Clin Anesth*, 2014 26(7): p. 511–6. [PubMed: 25439413]
85. Kuryshv YA, et al., Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. *J Pharmacol Exp Ther*, 2000 295(2): p. 614–20. [PubMed: 11046096]
86. Van't Klooster MP, et al., Local-anesthetic like inhibition of the cardiac sodium channel Nav1.5 alpha-subunit by 5-HT3 receptor antagonists. *Eur J Pharmacol*, 2016 789: p. 119–126. [PubMed: 27401036]
87. Kim MK, et al., Effect of the CYP2D6 genotype on the pharmacokinetics of tropisetron in healthy Korean subjects. *Eur J Clin Pharmacol*, 2003 59(2): p. 111–6. [PubMed: 12728290]
88. Candiotti KA, et al., The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? *Anesthesiology*, 2005 102(3): p. 543–9. [PubMed: 15731591]
89. Kaiser R, et al., Patient-tailored antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. *J Clin Oncol*, 2002 20(12): p. 2805–11. [PubMed: 12065557]
90. Bell GC, et al., Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clin Pharmacol Ther*, 2017 102(2): p. 213–218. [PubMed: 28002639]
91. Stamer UM, et al., CYP2D6- and CYP3A-dependent enantioselective plasma concentrations of ondansetron in postanesthesia care. *Anesth Analg*, 2011 113(1): p. 48–54. [PubMed: 21596874]
92. Perwitasari DA, et al., Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy. *Jpn J Clin Oncol*, 2011 41(10): p. 1168–76. [PubMed: 21840870]
93. Ashforth EI, et al., The pharmacokinetics of ondansetron after intravenous injection in healthy volunteers phenotyped as poor or extensive metabolisers of debrisoquine. *Br J Clin Pharmacol*, 1994 37(4): p. 389–91. [PubMed: 8018461]
94. He H, et al., Association of ABCB1 polymorphisms with the efficacy of ondansetron in chemotherapy-induced nausea and vomiting. *Clin Ther*, 2014 36(8): p. 1242–1252.e2. [PubMed: 25012726]
95. Babaoglu MO, et al., Association of the ABCB1 3435C>T polymorphism with antiemetic efficacy of 5-hydroxytryptamine type 3 antagonists. *Clin Pharmacol Ther*, 2005 78(6): p. 619–26. [PubMed: 16338277]
96. Tzvetkov MV, et al., Effects of OCT1 polymorphisms on the cellular uptake, plasma concentrations and efficacy of the 5-HT(3) antagonists tropisetron and ondansetron. *Pharmacogenomics J*, 2012 12(1): p. 22–9. [PubMed: 20921968]
97. Kaiser R, et al., Investigation of the association between 5-HT3A receptor gene polymorphisms and efficiency of antiemetic treatment with 5-HT3 receptor antagonists. *Pharmacogenetics*, 2004 14(5): p. 271–8. [PubMed: 15115912]
98. Tremblay PB, et al., Variations in the 5-hydroxytryptamine type 3B receptor gene as predictors of the efficacy of antiemetic treatment in cancer patients. *J Clin Oncol*, 2003 21(11): p. 2147–55. [PubMed: 12775740]

Figure 1.

Stylized diagram showing ondansetron metabolism and pharmacodynamics. Star symbols are used to indicate that CYP1A2 carries out the majority of ondansetron metabolism. A fully clickable version of this figure can be found at <https://www.pharmgkb.org/pathway/PA166179808>.

Figure 2.

Stylized diagram showing tropisetron metabolism and pharmacodynamics. Star symbols are used to indicate that CYP2D6 carries out the majority of tropisetron metabolism. A fully clickable version of this figure can be found at <https://www.pharmgkb.org/pathway/PA166179790>.